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(54) Title: LIPID ANALOGS FOR TREATING VIRAL INFECTIONS

(57) Abstract

A method of treating viral infections, and in particular HIV-1, hepatitis B virus, and herpesviruses, is disclosed. The method comprising administering to a subject in need of such treatment an infection-combating amount of a phospholipid or phospholipid derivative.

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LIPID ANALOGS FOR TREATING VIRAL INFECTIONS

Field of the Invention

This invention relates generally to the treatment of viral infections, and more specifically to the treatment of viral infections with phospholipids and phospholipid derivatives.

Background of the Invention

A current treatment for combating human immunodeficiency virus type 1 (HIV-1) infections is the administration of the nucleoside analog 3'-azido-3'-deoxythymidine (AZT) to an afflicted subject. See, e.g., U.S. Patent No. 4,724,232 to Rideout et al. HIV-1 infection treatment methods have also included the administration of ether lipid compounds in an amount effective to inhibit replication of the virus in infected cells, see, e.g., Kucera et al., AIDS Research and Human Retroviruses 6:491 (1990), and ether lipids conjugated with AZT and other antiviral nucleoside analogs. See PCT Application No. US91/04289 (published 26 December 1991). These compounds appear to act at the plasma membrane to block the endocytic process of HIV-1 into $CD4^+$ cells and the process of virus assembly, cell fusion and pathogenesis. They also can inhibit the activity of protein kinase C. Given the seriousness of HIV-1 infection worldwide, there is an ongoing need for new methods of combating HIV-1 infections.

Another virus of serious concern, hepatitis B virus (HBV), is one of a family of hepadnaviruses that cause acute and chronic liver disease, including liver cancer. HBV, which is found in the body fluids of infected persons, makes three antigenic proteins during multiplication in liver cells: hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and hepatitis B core antigen (HBcAg). These three virus antigenic proteins are important as markers for determining virus infection, as antibodies against the virus infection are made in response to these virus proteins in the blood. An HBV vaccine is available to prevent infection, and hyperimmune gamma globulin is available for temporary prophylaxis against developing HBV infection in

persons at risk. Clearly specific antiviral agents are needed for treatment and control of HBV infections in humans.

Based on the foregoing, it is an object of the present invention to provide a new treatment method for combating the effects of HIV-1.

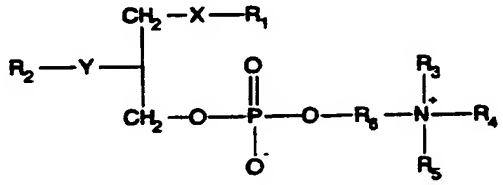
It is another object of the present invention to provide compounds and pharmaceutical compositions for carrying out HIV-1 treatment methods.

It is also an object of the present invention to provide a new treatment method for combating the effects of HBV.

It is a second object of the present invention to provide compounds and pharmaceutical compositions for carrying out HBV treatment methods.

Summary of the Invention

These and other objects are satisfied by the present invention, which provides methods of combating viral infections. As a first aspect, the present invention provides a method of combating a viral infection in a subject in need of such treatment comprising administering to the subject an effective infection-combating amount of a compound of Formula I or a pharmaceutical salt thereof.

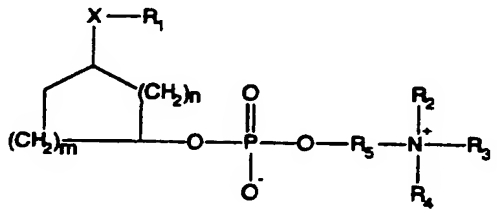


(I)

In the compounds of Formula I, R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic; X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic; Y is

selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; R_6 is a branched or unbranched C_2 to C_6 alkyl group; and R_3, R_4, and R_5 are independently methyl or ethyl, or R_3 and R_4 together form an aliphatic or heterocyclic ring having five or six members and R_5 is methyl or ethyl. Preferred compounds include 1-dodecanamido-2-decyloxypropyl-3-phosphocholine, 1-dodecanamido-2-octyloxypropyl-3-phosphocholine, and 1-dodecanamido-2-dodecyloxypropyl-3-phosphocholine. The method is particularly preferred as a treatment to combat viral infections caused by HIV-1, HBV, and herpes simplex virus. The present invention also includes pharmaceutical compositions comprising a compound of Formula I and a suitable pharmaceutical carrier.

As a second aspect, the present invention includes a method of combating viral infections in a subject in need of such treatment which comprises the administration to such a subject a compound of Formula II or a pharmaceutical salt thereof in an effective infection-combating amount.

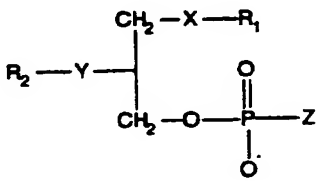


(II)

In Formula II, the ring structure is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl; R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group; R_2, R_3, and R_4 are independently methyl or ethyl, or R_2 and R_3 together form an aliphatic or heterocyclic ring having five or six members and R_4 is methyl or ethyl; X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; R_5 is a branched or unbranched C_2 to C_6 alkyl group; *m* is 1 to 3; and *n* is 0 to 2. Preferred compounds of Formula II are 3-hexadecanamido-cyclohexylphosphocholine and 3-hexadecylthio-cyclohexylphosphocholine.

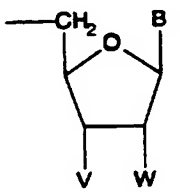
Adminstration of the compounds of Formula II is particularly useful in treating viral infections caused by HIV-1, HBV, and herpesviruses. The present invention also includes pharmaceutical compositions comprising a compound of Formula II and a suitable pharmaceutical carrier.

A third aspect of the present invention is a method of treating viral infections comprising administering to a subject in need of such treatment an effective infection-inhibiting amount of a compound of Formula III.



(III)

In compounds of Formula III, R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic; X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic; Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; and Z is a moiety of the Formula V,



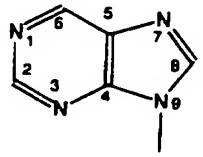
(V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

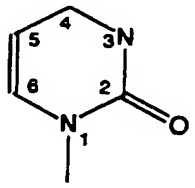
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with =O -OH, -SH, $-NH_2$, or halogen, at position 4 with NH_2 or =O, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII

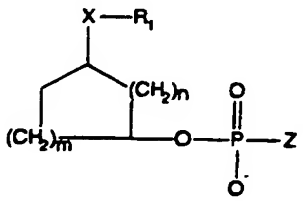


(VII)

substitued at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.

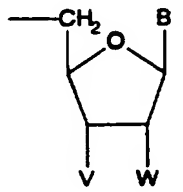
Pharmaceutical compositions comprising these compounds and a pharmaceutical carrier are also encompassed by the present invention.

A fourth aspect of the present invention is a method of inhibiting viral infections comprising administering to a subject in need of such treatment an effective infection-inhibiting amount of a compound of Formula IV.



(IV)

In the compounds of Formula IV, the ring structure is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl; R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group; X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; *m* is 1 to 3; *n* is 0 to 2; and Z is a moiety of the Formula V,



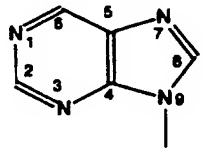
(V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

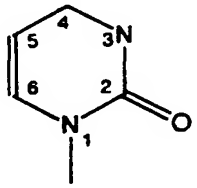
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with =O -OH, -SH, $-NH_2$, or halogen, at position 4 with NH_2 or =O, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII



(VII)

substitued at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.

The present invention also includes pharmaceutical compositions comprising a compound of Formula IV and a suitable pharmaceutical carrier.

Detailed Description of the Invention

As used herein, the term "alkyl" is intended to refer to an unbranched or branched alkyl group comprising carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, hexyl, and octyl. The term "pharmaceutical salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart undesired toxicological effects thereto. Examples of such salts are (a) salts formed with cations such as sodium, potassium, NH_4^+, magnesium, calcium polyamines, such as spermine, and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine.

A first aspect of the present invention is a method of combating viral infection comprising administering a compound of Formula I, wherein R_1, R_2, R_3, R_4, R_5, R_6, X, and Y are defined as stated above, or a pharmaceutical salt thereof. The amphipathic compounds of Formula I, which are generally analogs of phosphatidylcholine, include a glycerol backbone (represented by the chain of three carbon atoms to which other functional groups are bonded), lipophilic moieties (represented by R_1 and R_2) bonded to positions 1 and 2 of the glycerol backbone through functional groups (represented by X and Y) that are generally resistant to phospholipase degradation, and polar phosphate and quaternary amine groups (linked to one another through a short

alkyl group) bonded to position 3 of the glycerol backbone. Each of these components of the compounds of Formula I is described separately below.

In Formula I, as described above, R_1 is a lipophilic moiety; the lipophilicity of R_1 allows the compounds of Formula I to bind with the cell membrane of a cell infected with a retrovirus to provide an anchor thereto. R_1 can be an unbranched or branched, saturated or unsaturated C_6 to C_{18} alkyl group. Preferably, R_1 is an unbranched saturated or unsaturated C_8 to C_{12} alkyl group, and more preferably, R_1 is an unbranched saturated C_{10} or C_{12} alkyl group.

In compounds of Formula I, X is a functional group that links the lipophilic moiety R_1 and the glycerol backbone of the compound. X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; these functional groups are resistant to the hydrolytic activity of cellular lipases, in particular phospholipase A, which is specific for ester linkages at position 1 (as are present in phosphatidyl choline). Preferably, X is S or NHCO, with NHCO being most preferred.

In Formula I, R_2 is a lipophilic moiety which, as is true for R_1, enables the compounds of Formula I to bind with the cell membrane of an infected cell. R_2 can be an unbranched or branched, saturated or unsaturated C_6 to C_{14} alkyl group. Preferably, R_2 is an unbranched saturated or unsaturated C_8 to C_{12} alkyl group, and more preferably, R_2 is an unbranched saturated C_8 or C_{10} alkyl group. It is also preferred that R_1 and R_2 together contain between 18 and 22 carbon atoms.

R_2 is bonded to position 2 of the glycerol backbone through a functional group Y, which is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3. Like X, Y should be a moiety that is resistant to the hydrolytic activity of cellular lipases, and in particular phospholipase B, as this enzyme is specific for ester linkages at position 2. Preferably, X is S or O, with O being more preferred.

The polar hydrophilic end of the amphipathic compounds of Formula I, which can play a role in membrane interaction, comprises an amphoteric phosphoalkyl quaternary amine group in which the phosphate moiety carries

the negative charge and the quaternary amine moiety carries the positive charge. In this group, R_6, which is a branched or unbranched, saturated or unsatured C_2 to C_6 alkyl group, is preferably saturated C_2. R_3, R_4, and R_5 are independently selected from the group consisting of methyl and ethyl, with methyl being preferred, and with R_3, R_4, and R_5 each being methyl being more preferred, or R_3 and R_4 together form an aliphatic or heterocyclic ring having five or six members and R_5 is methyl or ethyl.

Exemplary compounds of Formula I include 1-dodecanamido-2-decyloxypropyl-3-phosphocholine (CP-128), 1-dodecanamido-2-octyloxypropyl-3-phosphocholine (CP-130), 1-dodecanamido-2-dodecyloxypropyl-3-phosphocholine (CP-131), and 1-dodecyloxy-2-decyloxypropyl-3-phosphocholine (CP-129). These compounds of Formula I can be synthesized according to the procedures set forth in Examples 1 and 2 below. Other compounds of Formula I can be synthesized using the same method with the appropriate reagents substituted for those listed.

Another aspect of the invention is a method of combating viral infection by administering compounds of Formula II, wherein R_1, R_2, R_3, R_4, R_5, X, *m*, and *n* are defined as stated above, or a pharmaceutical salt thereof. Compounds of Formula II are amphipathic moieties having a lipophilic moiety (represented by R_1) linked to a five- or six-membered ring structure (which is optionally sustituted 1 to 3 times with C_1 to C_3 alkyl) and a hydrophilic moiety that includes phosphate and quaternary amine groups linked by a short alkyl group that is bonded to the ring structure through the phosphate group. The hydrophilic group is linked to the ring at position 1, and the lipophilic group is linked to the ring at positions 2, 3, or 4. Like the compounds of Formula I, the compounds of Formula II are analogs of phosphatidyl choline. However, the ring structure provides a more conformationally restricted framework for the compound than compounds lacking a ring structure; this restricted framework can provide the compound with more favorable interaction with the cellular membrane and thereby increase its efficacy.

In the compounds of Formula II, R_1 can be an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group. As with the compounds of Formulas II, R_1 is a lipophilic moiety which binds with the cell membrane of infected cells to provide an anchor thereto. Preferably, R_1 is unbranched saturated or unsaturated C_{10} to C_{18} alkyl. More preferably, R_1 is unbranched saturated or unsaturated C_{16} to C_{18} alkyl.

In compounds of Formula II, X is a functional group that links the lipophilic moiety R_1 to position 1 of the ring structure. X should be a functional group, such as NHCO, CH_3NCO, CONH, $CONCH_3$, NH, NCH_3, S, SO, SO_2, or O, that is able to withstand the hydrolytic activity of cellular lipases. Preferably, Y is S or NHCO.

As stated above, the polar hydrophilic end of the amphipathic compounds of Formula II comprises a phosphate group bonded to the ring structure, a short alkyl group R_5 linked at one end thereto, and a quaternary amine group linked to the opposite end of the short alkyl group. R_5 is a saturated or unsaturated, branched or unbranched C_2 to C_6 alkyl group, and is more preferably C_2. R_2, R_3, and R_4 are independently selected from the group consisting of methyl and ethyl, with methyl being preferred, or R_2 and R_3 together form an aliphatic or heterocyclic five- or six-membered ring structure and R_4 is methyl or ethyl. It is more preferred that R_2, R_3, and R_4 are each methyl.

In the compounds of Formula II, *m* can be 1, 2, or 3, and *n* can be 0, 1, or 2. Preferably the ring structure is a five- or six-membered ring; thus, preferably *m* is 2 or 3 when *n* is 0, *m* is 1 or 2 when *n* is 1, and *m* is 1 when *n* is 2. As noted above, the ring structure provides conformational rigidity to the compound.

Exemplary compounds of Formula II include 3-hexadecylthio-cyclohexylphosphocholine (INK-1), 3-hexadecanamido-cyclohexylphosphocholine, 3-hexadecanamido-cyclopentylphosphocholine, and 3-hexadecylthio-cyclopentylphosphocholine. These compounds of Formula II can be synthesized by following the teachings of Example 3 below in combination with procedures known to those skilled in the art.

An additional aspect of the present invention is a method of combating viral infection with compounds of Formulas III and IV. These compounds substitute a moiety Z for the alkyl-quaternary amine of the compounds of Formulas I and II, wherein Z is as defined above. Z is a moiety that has demonstrated anti-viral activity by itself; thus conjugation of Z to the remainder of the compounds of Formulas III and IV provides a compound that potentially includes multiple active sites for viral inhibition.

In the compounds of Formula III, R_1, R_2, X and Y are defined above. R_1 is a lipophilic moiety; the lipophilicity of R_1 allows the compounds of Formula I to bind with the cell membrane of a cell infected with a retrovirus to provide an anchor thereto. R_1 can be an unbranched or branched, saturated or unsaturated C_6 to C_{18} alkyl group. Preferably, R_1 is an unbranched saturated or unsaturated C_8 to C_{12} alkyl group, and more preferably, R_1 is an unbranched saturated C_{10} or C_{12} alkyl group.

In compounds of Formula III, X is a functional group that links the lipophilic moiety R_1 and the glycerol backbone of the compound. X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; these functional groups are resistant to the hydrolytic activity of cellular lipases, in particular phospholipase A, which is specific for ester linkages at position 1 (as are present in phosphatidyl choline). Preferably, X is S or NHCO, with NHCO being most preferred.

In Formula III, R_2 is a lipophilic moiety which, as is true for R_1, enables the compounds of Formula III to bind with the cell membrane of an infected cell. R_2 can be an unbranched or branched, saturated or unsaturated C_6 to C_{14} alkyl group. Preferably, R_2 is an unbranched saturated or unsaturated C_8 to C_{12} alkyl group, and more preferably, R_2 is an unbranched saturated C_8 or C_{10} alkyl group. It is also preferred that R_1 and R_2 together contain between 18 and 22 carbon atoms.

R_2 is bonded to position 2 of the glycerol backbone through a functional group Y, which is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3. Like X, Y should be a moiety that is resistant to the hydrolytic activity of cellular

lipases, and in particular phospholipase B, as this enzyme is specific for ester linkages at position 2. Preferably, X is S or O, with O being more preferred.

In the compounds of Formula III, Z is a moiety of Formula V. Moieties of Formula V are intended to be anti-viral agents, and thus potentially provide an additional active site for anti-viral activity that may act through a different mechanism. In the moieties of Formula V, V is H, or N_3, or V and W together from a covalent bond with H and N_3 being preferred. W is H or F, with H being preferred.

In the compounds of Formula III, B is a purinyl moiety of Formula VI or a pyrimidinyl moiety of Formula VII, each of which are substituted as described above. As used herein, a purinyl moiety comprises six- and five-membered aromatic rings having the molecular structure illustrated in Formula VI. Those skilled in this art will appreciate that the double bonds illustrated in Formula VI are present to represent that the purinyl moieties have aromatic character, and that these double bonds may shift their positions in certain compounds due to the presence of certain substituents to retain the aromatic character of the moiety; in particular, those moieties having =O or NH_2 substituents at positions 2 and 4, such as adenine, guanine, xanthine, and hypoxanthine, are generally illustrated as having double bonds shifted from the positions shown in Formula VI. Similarly, as used herein a pyrimidinyl moiety comprises a six-membered aromatic ring having the molecular structure illustrated in Formula VII. Those skilled in this art will appreciate that the double bonds illustrated in Formula VII are included therein to represent that the moieties of Formula VII have aromatic character, and that these double bonds may shift for certain substituents, in particular for =O and NH_2 at positions 2 and 4, in order for the moiety to retain its aromatic character. Preferably, B is selected from the group consisting of adenine, thymine, cytosine, guanine, hypoxanthine, uracil, 5-fluorouracil, 2-fluoro-adenine, 2-chloro-adenine, 2-bromo-adenine, and 2-amino-adenine.

Preferably, Z is 3'-azido-3'-deoxythymidine, dideoxyinosine, dideoxycytidine, or 2', 3'-didehydro-3'-deoxythymidine. An exemplary

preferred compound of Formula III is 3'-azido-3'-deoxy-5'-(3-dodecanamido-2-decyloxypropyl)-phosphothymidine.

A further aspect of the present invention is a method of inhibiting viral infections comprising administering to a subject an effective infection-inhibiting amount of a compound of Formula IV, wherein R_1, R_2, X, m, n, and Z are as defined above. In the compounds of Formula IV, R_1 can be an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group. As with the compounds of Formula II, R_1 is a lipophilic moiety which binds with the cell membrane of infected cells to provide an anchor thereto. Preferably, R_1 is unbranched saturated or unsaturated C_{10} to C_{18} alkyl. More preferably, R_1 is unbranched saturated or unsaturated C_{16} to C_{18} alkyl.

In compounds of Formula IV, X is a functional group that links the lipophilic moiety R_1 to position 1 of the ring structure. X should be a functional group, such as NHCO, CH_3NCO, CONH, $CONCH_3$, NH, NCH_3, S, SO, SO_2, or O, that is able to withstand the hydrolytic activity of cellular lipases. Preferably, X is S or NHCO.

As stated above, the polar hydrophilic end of the amphipathic compounds of Formula IV comprises a phosphate group bonded to the ring structure and a moiety Z as defined in Formula V. In the moieties of Formula V, V is H, or N_3, or V and W together form a covalent bond, with H and N_3 being preferred. W is H or F, with H being preferred.

In the compounds of Formula IV, B is a purinyl moiety of Formula VI or a pyrimidinyl moiety of Formula VII, each of which are substituted as described above. As used herein, a purinyl moiety comprises six- and five-membered aromatic rings having the molecular structure illustrated in Formula VI. Those skilled in this art will appreciate that the double bonds illustrated in Formula VI are present to represent that the purinyl moieties have aromatic character, and that these double bonds may shift their positions in certain compounds due to the presence of certain substituents to retain the aromatic character of the moiety; in particular, those moieties having $=O$ or NH_2 substituents at positions 2 and 4, such as adenine, guanine, xanthine, and hypoxanthine, are generally illustrated as having double bonds shifted

from the positions shown in Formula VI. Similarly, as used herein a pyrimidinyl moiety comprises a six-membered aromatic ring having the molecular structure illustrated in Formula VII. Those skilled in this art will appreciate that the double bonds illustrated in Formula VII are included therein to represent that the moieties of Formula VII have aromatic character, and that these double bonds may shift for certain substituents, in particular for $=O$ and NH_2 at positions 2 and 4, in order for the moiety to retain its aromatic character. Preferably, B is selected from the group consisting of adenine, thymine, cytosine, guanine, hypoxanthine, uracil, 5-fluorouracil, 2-fluoro-adenine, 2-chloro-adenine, 2-bromo-adenine, and 2-amino-adenine.

Preferably, Z is selected from the group consisting of 3'-azido-3'-deoxythymidine, dideoxyinosine, dideoxycytidine, and 2', 3'-didehydro-3'-deoxythymidine.

In the compounds of Formula IV, *m* can be 1, 2, or 3, and *n* can be 0, 1, or 2. Preferably, the ring structure is a five- or six-membered ring; thus *m* is 2 or 3 when *n* is 0, *m* is 1 or 2 when *n* is 1, and *m* is 1 when *n* is 2. The ring structure provides conformational rigidity to the compound.

An exemplary compound of Formula IV is 3'-azido-3'-deoxy-5'-(3-hexadecylthiocyclohexyl)-phosphothymidine.

Experimentation has demonstrated the efficacy of the compounds of Formulas I, II, III and IV in combating viral infection. For example, compounds CP-128, CP-129, CP-130, CP-131, and INK-1 in nanomolar concentration substantially inhibit the HIV-1 activity in CEM-SS cells. Further, these compounds did so at noncytotoxic levels, thus indicating their promise as therapeutic agents for treatment of viral infections. The compounds of Formulas I, II, III and IV are believed to attach to the cell membrane and thus are particularly effective against infections caused by membrane-containing or envelope-containing viruses, as these viruses typically require access to the cell membrane to multiply and assemble through the manufacture of new viral particles. For example, the compounds of Formulas I, II, III and IV can inhibit the transport and/or incorporation of HIV-1 major glycoprotein gp120 in the cell membrane of an infected cell prior to viral assembly. Such

inhibition can block the transmission of infectious HIV-1 into neighboring cells. In addition, compounds of Formulas I, II, III and IV can inhibit the production of the HBV core and "e" antigens, each of which contribute to the assembly of new virus particles and the spread of HBV infection. Other infections for which the compounds of Formulas I, II, III and IV should be efficious include those caused by other membrane-containing or envelope-containing herpesviruses, influenza, respiratory syncytial virus, mumps, measles, and parainfluenza viruses.

Experimentation has also shown that the compounds of Formulae I, II, III, and IV have potent anti-tumor activity. In particular, some of these compounds have IC_{50} values of approximately 1.2 μM against the KB-cell line.

In the manufacture of a medicament according to the invention, hereinafter referred to as a "formulation," the compounds of Formulas I, II, III and IV are typically admixed with, among other things, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.5 percent to 95 percent by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

The formulations of the invention include those suitable for oral, rectal, topical, intrathecal, buccal (e.g., sub-lingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as

a solution or a suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above).

Suitable solid diluents or carriers for the solid oral pharmaceutical dosage unit forms are selected from the group consisting of lipids, carbohydrates, proteins and mineral solids, for example, starch, sucrose, lactose, kaolin, dicalcium phosphate, gelatin, acacia, corn syrup, corn starch, talc and the like.

Capsules, both hard and soft, are filled with compositions of these active ingredients in combination with suitable diluents and excipients, for example, edible oils, talc, calcium carbonate and the like, and also calcium stearate.

In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Liquid preparations for oral administration are prepared in water or aqueous vehicles which advantageously contain suspending agents, for example, methylcellulose, acacia, polyvinylpyrrolidone, polyvinyl alcohol and the like.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavored base, usually sucrose

and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin, glycerin, sucrose, or acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, intrathecal, or intradermal injection. The formulation should be sufficiently fluid that for easy parental administration. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Such preparations should be stable under the conditions of manufacture and storage, and ordinarily contain in addition to the basic solvent or suspending liquid, preservatives in the nature of bacteriostatic and fungistatic agents, for example, parabens, chlorobutanol, benzyl alcohol, phenol, thimerosal, and the like. In many cases, it is preferable to include osmotically active agents, for example, sugars or sodium chloride in isotonic concentrations. Injectable formulations according to the invention generally contain from 0.1 to 5 percent w/v of active compound and are administered at a rate of 0.1 ml/min/kg.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15 percent w/w, for example, from 0.5 to 2 percent w/w.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis

of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered aqueous solution of, for example, 0.1 to 0.2M concentration with respect to the said active compound.

Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, Pharmaceutical Research 3 (6), 318, (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis\tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

The compounds of Formulas I, II, III and IV are administered in an amount sufficient to combat viral infection. The dose can vary depending on the compound selected for administration, the subject, the route of administration, and other factors. Preferably, the compound is administered in an amount of at least 0.1 ng/kg, 1 ng/kg, 0.001 μg/kg or more, and is adminstered in an amount no greater than 0.1 g/kg, 0.01 g/kg, 1 mg/kg, or less.

The invention is illustrated in greater detail in the following nonlimiting examples. In the Examples, "g" means grams, "mg" means milligrams, "μg" means micrograms, "μM" means micromolar, "mL" means milliliters, "°C" means degrees Celsius, "THF" means tetrahydrofuran, "DMF" means dimethylformamide, "mol" means moles, "mmol" means millimoles, and "psi" means pounds per square inch.

EXAMPLE 1

Preparation of Amidoalkyl Derivatives

The procedure set forth below was used to prepare the following compounds:

(a) 1-dodecanamido-2-decyloxypropyl-3-phosphocholine (CP-128)

(b) 1-dodecanamido-2-octyloxypropyl-3-phosphocholine (CP-130)

(c) 1-dodecanamido-2-dodecyloxypropyl-3-phosphocholine (CP-131)

3-Amino-1,2-propanediol was reacted with lauroyl chloride at room temperature in pyridine and dimethyl formamide. The resulting dodecanamido propanediol was recrystallized from chloroform, then reacted with triphenylmethyl chloride. The tritylated product was recrystallized from hexanes. The C-2 hydroxyl was alkylated by reaction with sodium hydride and the appropriate alkyl bromide in tetrahydrofuran for formation of the ether linkage at C-2 (1-bromodecane for CP-128; 1-bromooctane for CP-130; 1-bromododecane for CP-131). Column chromatography on silica gel with a discontinuous gradient of hexanes:ethyl acetate (95:5 to 80:20) produced the desired 1-dodecanamido-2-alkoxy-3-trityloxypropane. Detritylation with p-toluensulfonic acid in 5:1 methylene chloride:methanol gave product having a free primary hydroxyl after column chromatography (hexanes:ethyl acetate 95:5 to 0:100). Reaction with 2-bromoethyl phosphodichloridate in diethyl ether and pyridine produced the phosphate ester, which was purified on silica gel with chloroform:methanol (100:0 to 2:1). Displacement of the bromide with aqueous trimethylamine in chloroform:isopropanol:dimethyl formamide (3:5:5) gave the final phosphocholine product after column chromatography with chloroform:methanol:ammonium hydroxide (70:35:1 to 70:35:7).

EXAMPLE 2

Preparation of 1-dodecyloxy-2-decyloxypropyl-3-phosphocholine (CP-129)

Isopropylidene glycerol was alkylated using potassium hydroxide and 1-bromododecane in toluene. The resulting ketal was hydrolyzed with hydrochloric acid in methanol, and the diol formed thereby was recrystallized from methanol. The remaining reaction steps (tritylation, alkylation, detritylation, phosphorylation, amination) followed the procedures described above in Example 1 for the alkylamido derivatives.

EXAMPLE 3

Preparation of cis- and trans-3-hexadecylthio-cyclohexylphosphocholine (INK-1)

2-Cyclohexenone (0.14 mol, 13.4 mL) was dissolved in 10 mL of 10 percent sodium hydroxide and 50 mL of THF. An equimolar amount of hexadecyl mercaptan (0.14 mol, 42.9 mL) was added to the unsaturated ketone and the mixture refluxed to produce 3-hexadecylthiocyclohexanone

(70 percent yield). This product (5.23 mmol, 1.851 g) was dissolved in methanol and reduced with sodium borohydride (5.23 mmol, 0.199 g) to give a racemic mixture of 3-hexadecylthiocyclohexanol (yield 62 percent; cis:trans ratio 4:1). The phosphorylating agent was prepared by refluxing phosphorus oxychloride (0.65 mol, 60.8 mL) and 2-bromoethanol (0.38 mol, 27.0 mL) in 25 mL of trichloroethylene to produce 2-bromoethyl dichlorophosphate (yield 53 percent). The 3-hexadecylthiocyclohexanol (0.56 mmol, 0.200 g) was dissolved in diethyl ether:THF (2:1) and refluxed with the 2-bromoethyl dichlorophosphate (222 mmol, 0.3 mL) to produce 3-hexadecylthiocyclohexyl phosphoethyl bromide (yield 54 percent). The latter (0.276 mmol, 0.150 g) was dissolved in isopropyl alcohol chloroform:DMF (5:3:5) and heated at 65°C with trimethylamine (0.042 mol, 2 mL) to produce the desired product, 3-hexadecylthiocyclohexyl-phosphocholine (yield 38 percent).

This procedure can also be used to prepare 3-alkylthio-cyclopentyl derivatives by substituting 2-cyclopentenone.

EXAMPLE 4

Preparation of cis- and trans-3-hexadecanamido-cyclohexylphosphocholine

2-Cyclohexenone is reacted with benzylamine to give 3-benzylaminocyclohexanone. Hydrogenolysis of the benzylamino group then gives 3-aminocyclohexanone. Reaction with hexadecanoyl chloride affords 3-hexadecanamidocyclohexanone, which is then reduced with sodium borohydride to produce a cis/trans mixture of 3-hexadecanamidocyclohexanol. Separation by column chromatography then gives the pure isomers. Reaction with bromoethylphosphodichloridate, then with trimethylamine will produce 3-hexadecanamido-cyclohexylphosphocholine.

Synthesis of the 2- and 4-alkylamido derivatives can be carried out following essentially similar procedures with the substitution of appropriate starting materials.

EXAMPLE 5

Preparation of 3'-azido-3'-deoxy-5'-(dodecanamido-2-decoxypropyl)-phosphothymidine

3-Dodecanamido-2-decoxy-propanol was synthesized via the scheme described in Morris-Natschke et al., C.J. Med. Chem. 29:2114 (1986). This alcohol was phosphorylated with diphenyl chlorophosphate in pyridine to give the corresponding phospate ester. The phenyl groups were then removed via hydrogenolysis with PtO_2. The phosphatidic acid derivatives were then conjugated to the 5'-hydroxyl of AZT (DCC condensation).

EXAMPLE 6

Preparation of 3'-azido-3'-deoxy-5'-(dodecyoxy-2-decyloxypropyl)-phosphothymidine

A. **3-Dodecyloxy-1,2-propanediol**

Isopropylideneglycerol (solketal, 26.4 g, 0.20 mol) in 60 mL of tolune was added dropwise to a solution of powdered KOH (22.4 g., 0.04 mol) in 150 mL toluene. The resulting mixture was refluxed for 4 hours. 1-Bromododecane (50 g, 0.20 mol) in 40 mL of tolune was then added dropwise, and the solution was refluxed for 10 hours. After cooling, the reaction mixture was diluted with 200 mL of ice-water and extracted with diethyl ether (3 X 100 mL). The ether layers were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was dissolved in 60 mL of diethyl ether and 260 mL of MeOH. Concentrated HCl (60 mL) was added, and the solution was refluxed for 16 hours. After cooling, ice-water (150 mL) was added, and the layers were separated. The aqueous layer was extracted with diethyl ether (2 X 75 mL). The combined organic fractions were then dried over sodium sulfate, filtered, and concentrated *in vacuo*. The solid residue was recrystallized from MeOH to give 37 g (0.14 mol, 71%) of a white solid.

B. **3-Dodecyloxy-1-triphenylmethoxy-2-propanol**

The diol synthesized in Section A was tritylated with trityl chloride (59 g, 0.21 mol) in pyridine (200 mL) at 70°C for 5 hours and then at room temperature overnight. The pyridine was removed under vacuum, and the solid residue was partitioned between water and $CHCl_3$. The $CHCl_3$ layer

was washed with 5 percent HCl and water, then dried over magnesium sulfate. After removal of solvent, the product was recrystallized from hexanes:ethyl acetate (10:1) to give 19 g of pure product.

C. 3-Dodecyloxy-2-decyloxy-1-triphenylmethoxypropane

The trityl ether of Section B (13.5 g, 0.027 mol) was added dropwise to an ice-cooled suspension of sodium hydride (80%, 1.6 g, 0.054 mol) in 150 mL of tetrahydrofuran under nitrogen. After stirring for 2 hours at room temperature, heat was applied (55°C). 1-Bromodecane (6 g, 0.027 mol) was added dropwise; heating was continued for 6 hours. After cooling for 3 hours, water was added slowly. Diethyl ether (2 X 100 mL) was added, and the solution washed with 15 percent sodium thiosulfite, water, and brine. After drying over sodium sulfate, the ether was removed, and the residue was chromatographed with a gradient of hexanes:ethyl acetate (100:0 to 20:1) to give 9 g (52%) of a clear liquid.

D. 3-Dodecyloxy-2-decyloxy-1-propanol

Detritylation of the product of Section C was accomplished using *p*-toluenesulfonic acid (0.9 g) in $CHCl_3$:MeOH (72 mL:36 mL) (stirred at room temperature for 48 hours, added 10 percent sodium bicarbonate, extracted with $CHCl_3$, dried over magnesium sulfate, and concentrated). The residue was purified by column chromatography using a gradient of hexanes:ethyl acetate (20:1 to 5:1) to give 3.5 g (63%) of pure 3-dodecyloxy-2-decyloxy-1-propanol.

E. 3-Dodecyloxy-2-decyloxypropyl Diphenyl Phosphate

Diphenylchlorophosphate (0.7 mL, 3.4 mmol) in 10 mL of diethyl ether was cooled to 4°C under nitrogen. 3-Dodecyloxy-2-decyloxy-1-propanol (1.0 g, 2.6 mmol) in 15 mL of pyridine and 5 mL of diethyl ether was added. The solution was warmed to room temperature then heated to about 52°C for 3 hours. It was then cooled to room temperature, diluted with 50 mL of diethyl ether, and washed with water (2 X 25 mL), 0.5 N HCl (25 mL), and then water (25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to an oil. Chromatography with a

gradient of hexanes:ethyl acetate (10:1 to 1:1) produced 980 mg (1.5 mmol, 60%) of pure product.

F. **3-Dodecyloxy-2-decyloxpropyl Phosphate**

PtO_2 (69 mg) was placed in a Parr hydrogenation bottle. The diphenyl phosphate of Section E (500 mg) in 100 mL of EtOH was then added. The reaction mixture was hydrogenated at 15 psi for 1.5 hours until hydrogen uptake ceased. The reaction mixture was then filtered through Celite, and the EtOH was removed *in vacuo*. The oil was dissolved in 25 mL of pyridine, concentrated *in vacuo*, and dried under high vacuum to give 350 mg of pure solid phosphatidic acid.

G. **3'-Azido-3'-deoxy-5'-(3-dodecyloxy-2-decyloxypropyl)-phosphothymidine**

AZT (43 mg, 0.16 mmol) and the phosphatidic acid of Section F (105 mg, 0.22 mmol) were azeotropically dried with pyridine (3 X 3 mL) by *in vacuo* removal. Dicyclohexylcarbodiimide (220 mg, 1.07 mmol) was added, and the drying was repeated 4 times. A final 3 mL portion of pyridine was added, and the reaction mixture was stirred at room temperature in a desiccator for 4 days. Water (1 g) was added, and the mixture was stirred for 4 hours. The solvents were removed *in vacuo*, and the crude material was chromatographed on 2 g of silica gel using a gradient of $CHCl_3$:MeOH (15:1 to 2:1). The product was dissolved in 11 mL of $CHCl_3$:MeOH:H_2O (4:6:1) and stirred with 1.5 g of Whatman preswollen microgranular cation (Na^+) exchange concentrated *in vacuo* to give 37 mg of product (22%). FAB ms showed a [MH + Na] ion at 752.4350 ($C_{35}H_{64}N_5O_9PNa$, 1.4 ppm) and a $[M+2Na]^+$ ion at 774.4179 ($C_{35}H_{63}N_5O_9PNa_2$, 2.0 ppm).

EXAMPLE 7

Procedure for Assessing Anti-HIV-1 Activity

The inhibitory effects of synthetic phospholipid compounds on the replication of human immunodeficiency virus type 1 (HIV-1) virus in cells was examined by the plaque assay procedure of L. Kucera et al., Aids Research and Human Retroviruses 6, 491 (1990). In brief, CEM-SS cell monolayers were infected with HIV-1. Infected cells were overlaid with RPMI-1640 medium plus 10 percent fetal bovine serum (FBS) supplemented with different

concentrations of inhibitor. Plaques were counted at five days after infection. In this assay HIV-1 syncytial plaques are seen as large, multicellular foci (10 to 25 nuclei/syncytium) that appear either brown and granular or clear. Since the number of HIV-1 syncytial plaques correlates with reverse transcriptase (RT) and p24 core antigen activity in the HIV-1 infected cell overlay fluids, the syncytial plaque assay can be used to quantify the amount of infectious virus. Reverse transcriptase activity was assayed according to a described procedure (B. J. Poeisz et al., Proc. Natl. Acad. Scie. (U.S.A.) 77, 7415 (1980)). The activity of p24 core antigen induced by HIV-1 infection of CEM-SS cells was measured spectrophotometrically using the commercial Coulter EIA.

EXAMPLE 8

Results of Assessment of Anti-HIV-1 Activity

The results (Table 1) showed that all of the lipid compounds tested have an IC_{50} against HIV-1 syncytial plaque formation ranging from 0.11 to 0.64 μM. The compounds' IC_{50} for cell cytotoxicity ranged from 11.85 to 75.7 μM. The highest differential selectivity (611.7), which is a ratio of the cytotoxicity to the anti-HIV-1 activity, was obtained with compound CP-130.

Table 1

Evaluation of Ether Lipids for Cytotoxicity and Anti-Viral Activity in CEM-SS Cells

IC50 (μM)

Compounds	*Cytotoxicity*	*Anti-HIV-1 Activity*	*Differential Selectivity*
CP-128	31.6	0.14	225.7
CP-129	75.7	0.64	176.0
CP-130	67.2	0.11	611.7
CP-131	36.6	0.32	114.2
JM-1 (cis)	11.85	0.42	28.2

Cytotoxicity was measured by uptake of TdR-H^3 into total DNA in the presence of serial concentrations of compound.

Anti-HIV-1 activity was measured by standard plaque assay using CEM-SS cell monolayers.

Differential selectivity was determined by dividing the IC50 for cytotoxicity by the IC50 for anti-HIV-1 activity.

EXAMPLE 9

Assessment of HBV Activity Inhibition

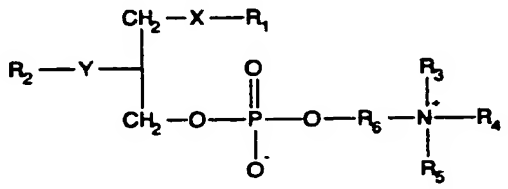
Human hepatoblastomas (HepG2) cells were tranfected with plasmid DNA containing tandem copies of HBV genomes. These cells constituitively replicate HBV particles. HepG2 cells were treated with varying concentrations of CP-128 to determine the toxic cell concentration (TC_{50}) by neutral red dye uptake. Also, the inhibitory concentration (IC_{50}) of CP-128 for HBV replication was determined by ELISA.

It was determined that CP-128 cytotoxicity (TC_{50}) was 61.7 μM and the anti-HIV-1 activity (IC_{50}) was 15.6 μM (Table 1). These data indicate that CP-128 has selective anti-HBV activity. Mechanism studies indicate that CP-128 can have an inhibitory effect on the cellular production of HBV-induced DNA, core antigen (HBcAg) and "e" antigen (HBeAg). As a result, it is postulated that CP-128 and other compounds of the present invention are likely inhibiting the assembly of HBV nucleocapids and the packaging of viral pregenomic DNA.

The foregoing examples are illustrative of the present invention and are not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

WHAT IS CLAIMED IS:

1. A method of combating a viral infection in a subject in need of such treatment comprising administering to said subject an effective infection-combating amount of a compound of Formula I



(I)

wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_6 is a branched or unbranched C_2 to C_6 alkyl group; and

R_3, R_4, and R_5 are independently methyl or ethyl, or R_3 and R_4 together form an aliphatic or heterocyclic ring having five or six members and R_5 is methyl or ethyl;

or a pharmaceutical salt thereof.

2. A method according to Claim 1, wherein R_1 is unbranched C_8 to C_{12} alkyl.

3. A method according to Claim 1, wherein R_1 is unbranched C_8-

4. A method according to Claim 1, wherein R_1 is unbranched C_{10}.

5. A method according to Claim 1, wherein R_1 is unbranched C_{12}.

6. A method according to Claim 1, wherein R_2 is unbranched C_8 to C_{12} alkyl.

7. A method according to Claim 1, wherein R_2 is unbranched C_8.

8. A method according to Claim 1, wherein R_2 is unbranched C_{10}.

9. A method according to Claim 1, wherein R_2 is unbranched C_{12}.

10. A method according to Claim 1, wherein X is NCO.

11. A method according to Claim 1, wherein X is S.

12. A method according to Claim 1, wherein Y is O.

13. A method according to Claim 1, wherein R_3, R_4, and R_5 are each methyl.

14. A method according to Claim 1, wherein said compound of Formula I is 1-dodecanamido-2-decyloxypropyl-3-phosphocholine.

15. A method according to Claim 1, wherein said compound of Formula I is 1-dodecanamido-2-octyloxypropyl-3-phosphocholine.

16. A method according to Claim 1, wherein said compound of Formula I is 1-dodecanamido-2-dodecyloxypropyl-3-phosphocholine.

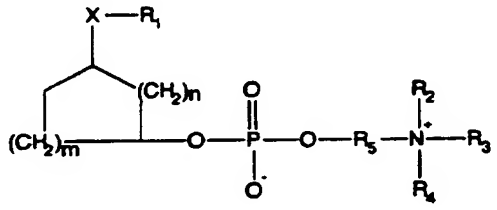
17. A method according to Claim 1, wherein said compound of Formula I is 1-dodecyloxy-2-decyloxypropyl-3-phosphocholine.

18. A method according to Claim 1, wherein said viral infection is caused by HIV-1 virus.

19. A method according to Claim 1, wherein said viral infection is caused by hepatitis B virus.

20. A method according to Claim 1, wherein said viral infection is caused by herpes simplex virus.

21. A method of combating a viral infection in a subject in need of such treatment comprising administering to said subject an effective infection-combating amount of a compound of Formula II:



(II)

wherein: the ring structure of Formula II is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl;

R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group;

R_2, R_3, and R_4 are independently methyl or ethyl, or wherein R_2 and R_3 together form an aliphatic or heterocyclic ring having five or six members and R_4 is methyl or ethyl;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_5 is a branched or unbranched C_2 to C_6 alkyl group;

m is 1 to 3; and

n is 0 to 2;

or a pharmaceutical salt thereof.

22. A method according to Claim 21, wherein R_1 is C_{10} to C_{18}.

23. A method according to Claim 21, wherein R_1 is C_{16} to C_{18}.

24. A method according to Claim 21, wherein R_2, R_3, and R_4 are each methyl.

25. A method according to Claim 21, wherein R_5 is C_2.

26. A method according to Claim 21, wherein *n* is 1.

27. A method according to Claim 21, wherein *m* is 2.

28. A method according to Claim 21, wherein said compound of Formula II is 3-hexadecylthio-cyclohexylphosphocholine.

29. A method according to Claim 21, wherein said compound of Formula II is 3-hexadecylthio-cyclopentylphosphocholine.

30. A method according to Claim 21, wherein said compound of Formula II is 3-hexadecanamido-cyclohexylphosphocholine.

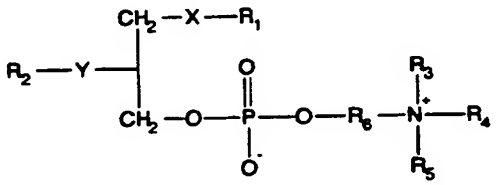
31. A method according to Claim 21, wherein said compound of Formula II is 3-hexadecanamido-cyclopentylphosphocholine.

32. A method according to Claim 21, wherein said viral infection is caused by the HIV-1 virus.

33. A method according to Claim 21, wherein said viral infection is caused by hepatitis B virus.

34. A method according to Claim 21, wherein said viral infection is caused by herpes simplex virus.

35. A method of inhibiting the production of a hepatitis B virus antigen, the antigen being selected from the group consisting of core antigen and "e" antigen, in a subject in need of such treatment comprising administering to said subject an effective antigen-inhibiting amount of a compound of Formula I



(I)

wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_6 is a branched or unbranched C_2 to C_6 alkyl group; and

R_3, R_4, and R_5 are independently methyl or ethyl, or R_3 and R_4 together form an aliphatic or heterocyclic ring having five or six members and R_5 is methyl or ethyl;

or a pharmaceutical salt thereof.

36. A method according to Claim 35, wherein R_1 is unbranched C_8 to C_{12} alkyl.

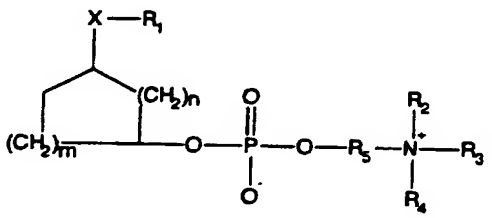
37. A method according to Claim 35, wherein R_2 is unbranched C_8 to C_{12} alkyl.

38. A method according to Claim 35, wherein X is NCO or S.

39. A method according to Claim 35, wherein Y is O.

40. A method according to Claim 35, wherein R_3, R_4, and R_5 are each methyl.

41. A method of inhibiting the production of a hepatitis B virus antigen, the antigen being selected from the group consisting of core antigen and "e" antigen, in a subject in need of such treatment comprising administering to said subject an effective antigen-inhibiting amount of a compound of Formula II



(II)

wherein: the ring structure of Formula II is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl;

R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group;

R_2, R_3, and R_4 are independently methyl or ethyl, or wherein R_2 and R_3 together form an aliphatic or heterocyclic ring having five or six members and R_4 is methyl or ethyl;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_5 is a branched or unbranched C_2 to C_6 alkyl group;

m is 1 to 3; and

n is 0 to 2;

or a pharmaceutical salt thereof.

42. A method according to Claim 41, wherein R_1 is C_{10} to C_{18}.

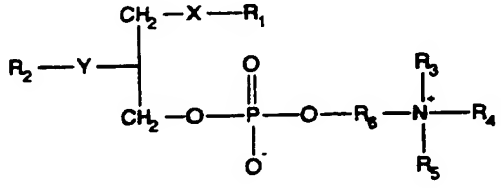
43. A method according to Claim 41, wherein R_2, R_3, and R_4 are each methyl.

44. A method according to Claim 41, wherein R_5 is C_2.

45. A method according to Claim 41, wherein *n* is 1.

46. A method according to Claim 41, wherein *m* is 2.

47. A method of inhibiting the incorporation of HIV-1 major glycoprotein gp120 into a cell membrane in a subject infected with HIV-1, comprising administering to said subject a compound of Formula I in an amount effective to inhibit such incorporation:



(I)

wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_6 is a branched or unbranched C_2 to C_6 alkyl group; and

R_3, R_4, and R_5 are independently methyl or ethyl, or R_3 and R_4 together form an aliphatic or heterocyclic ring having five or six members and R_5 is methyl or ethyl;

or a pharmaceutical salt thereof.

48. A method according to Claim 47, wherein R_1 is unbranched C_8 to C_{12} alkyl.

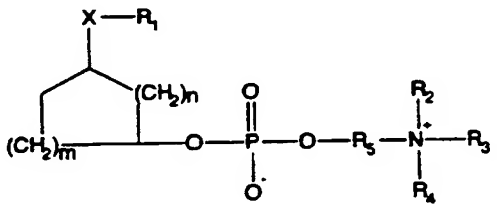
49. A method according to Claim 47, wherein R_2 is unbranched C_8 to C_{12} alkyl.

50. A method according to Claim 47, wherein X is NCO or S.

51. A method according to Claim 47, wherein Y is O.

52. A method according to Claim 47, wherein R_3, R_4, and R_5 are each methyl.

53. A method of inhibiting the incorporation of HIV-1 major glycoprotein gp120 into a cell membrane in a subject infected with HIV-1, comprising administering to said subject a compound of Formula II in an amount effective to inhibit such incorporation:



(II)

wherein: the ring structure of Formula II is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl;

R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group;

R_2, R_3, and R_4 are independently methyl or ethyl, or wherein R_2 and R_3 together form an aliphatic or heterocyclic ring having five or six members and R_4 is methyl or ethyl;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_5 is a branched or unbranched C_2 to C_6 alkyl group;

m is 1 to 3; and

n is 0 to 2;

or a pharmaceutical salt thereof.

54. A method according to Claim 53, wherein R_1 is C_{10} to C_{18}.

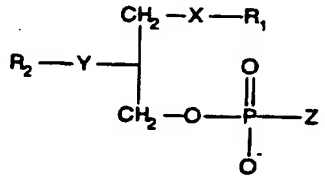
55. A method according to Claim 53, wherein R_2, R_3, and R_4 are each methyl.

56. A method according to Claim 53, wherein R_5 is C_2.

57. A method according to Claim 53, wherein *n* is 1.

58. A method according to Claim 53, wherein *m* is 2.

59. A method of combating a viral infection in a subject in need of such treatment comprising administering to said subject an effective infection-combating amount of a compound of Formula III



(III)

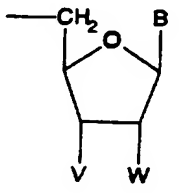
wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; and

Z is a moiety of the Formula V,



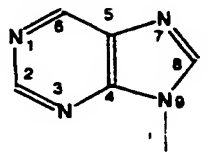
(V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

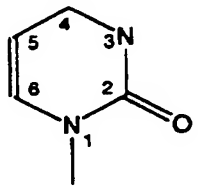
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with =O -OH, -SH, $-NH_2$, or halogen, at position 4 with NH_2 or =O, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII



(VII)

substitued at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen;

or a pharmaceutical salt thereof.

60. A method according to Claim 59, wherein R_1 is unbranched C_8 to C_{12} alkyl.

61. A method according to Claim 59, wherein R_1 is unbranched C_8.

62. A method according to Claim 59, wherein R_1 is unbranched C_{10}.

63. A method according to Claim 59, wherein R_1 is unbranched C_{12}.

64 A method according to Claim 59, wherein R_2 is unbranched C_8 to C_{12} alkyl.

65. A method according to Claim 59, wherein R_2 is unbranched C_8.

66. A method according to Claim 59, wherein R_2 is unbranched C_{10}.

67. A method according to Claim 59, wherein R_2 is unbranched C_{12}.

68. A method according to Claim 59, wherein X is NCO.

69. A method according to Claim 59, wherein X is S.

70. A method according to Claim 59, wherein Y is O.

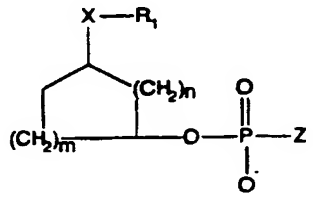
71. A method according to Claim 59, wherein B is selected from the group consisting of adenine, thymine, cytosine, guanine, xanthine, hypoxanthine, uracil, 5-fluoro-uracil, 2-fluoro-adenine, 2-chloro-adenine, 2-bromo-adenine, and 2-amino-adenine.

72. A method according to Claim 59, wherein said viral infection is caused by HIV-1 virus.

73. A method according to Claim 59, wherein said viral infection is caused by hepatitis B virus.

74. A method according to Claim 59, wherein said viral infection is caused by herpes simplex virus.

75. A method of combating a viral infection in a subject in need of such treatment comprising administering to said subject an effective infection-combating amount of a compound of Formula IV:



(IV)

wherein: the ring structure of Formula IV is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl;

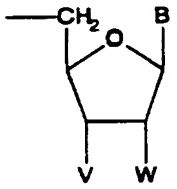
R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

m is 1 to 3;

n is 0 to 2; and

Z is a moiety of the Formula V,



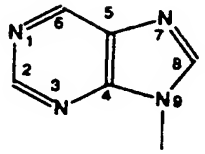
(V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

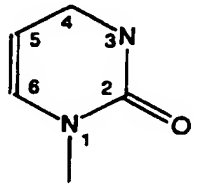
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with =O -OH, -SH, $-NH_2$, or halogen, at position 4 with NH_2 or =O, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII



(VII)

substitued at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen;

or a pharmaceutical salt thereof.

76. A method according to Claim 75, wherein R_1 is C_{10} to C_{18}.

77. A method according to Claim 75, wherein R_1 is C_{16} to C_{18}.

78. A method according to Claim 75, wherein R_5 is C_2.

79. A method according to Claim 75, wherein *n* is 1.

80. A method according to Claim 75, wherein *m* is 2.

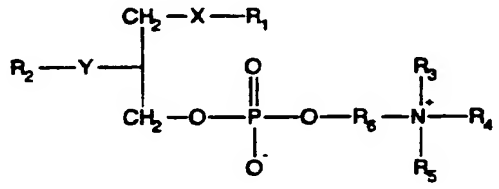
81. A method according to Claim 75, wherein B is selected from the group consisting of adenine, thymine, cytosine, guanine, xanthine, hypoxanthine, uracil, 5-fluoro-uracil, 2-fluoro-adenine, 2-chloro-adenine, 2-bromo-adenine, and 2-amino-adenine.

82. A method according to Claim 75, wherein said viral infection is caused by the HIV-1 virus.

83. A method according to Claim 75, wherein said viral infection is caused by hepatitis B virus.

84. A method according to Claim 75, wherein said viral infection is caused by herpes simplex virus.

85. A compound of Formula I



(I)

wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;
R_6 is a branched or unbranched C_2 to C_6 alkyl group; and
R_3, R_4, and R_5 are independently methyl or ethyl, or R_3 and R_4 together form an aliphatic or heterocyclic ring having five or six members and R_5 is methyl or ethyl.

86. A compound according to Claim 85, wherein R_1 is unbranched C_8 to C_{12} alkyl.

87. A compound according to Claim 85, wherein R_2 is unbranched C_8 to C_{12} alkyl.

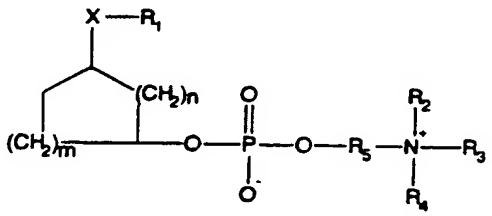
88. A compound according to Claim 85, wherein X is NCO or S.

89. A compound according to Claim 85, wherein Y is O.

90. A compound according to Claim 85, wherein R_3, R_4, and R_5 are each methyl.

91. A compound according to Claim 85, in combination with a pharmaceutical carrier.

92. A compound of Formula II



(II)

wherein: the ring structure of Formula II is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl;

R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group;

R_2, R_3, and R_4 are independently methyl or ethyl, or wherein R_2 and R_3 together form an aliphatic or heterocyclic ring having five or six members and R_4 is methyl or ethyl;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_5 is a branched or unbranched C_2 to C_6 alkyl group;

m is 1 to 3; and

n is 0 to 2.

93. A compound according to Claim 92, wherein R_1 is C_{10} to C_{18}.

94. A compound according to Claim 92, wherein R_2, R_3, and R_4 are each methyl.

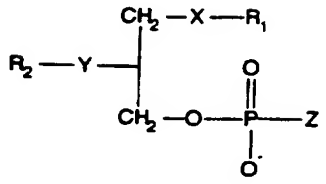
95. A compound according to Claim 92, wherein R_5 is C_2.

96. A compound according to Claim 92, wherein *n* is 1.

97. A compound according to Claim 92, wherein *m* is 2.

98. A compound according to Claim 92, in combination with a pharmaceutical carrier.

99. A compound of Formula III



(III)

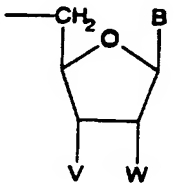
wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; and

Z is a moiety of the Formula V,



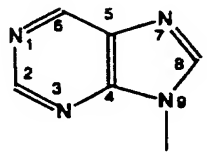
(V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

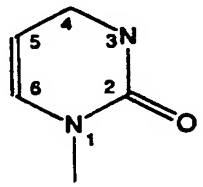
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with =O -OH, -SH, $-NH_2$, or halogen, at position 4 with NH_2 or =O, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII

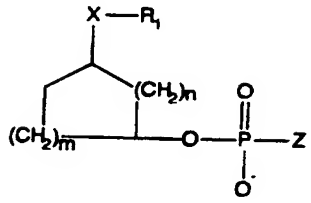


(VII)

substitued at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.

100. A compound of Claim 99, in combination with a pharmaceutical carrier.

101. A compound of Formula IV:



(IV)

wherein: the ring structure of Formula IV is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl;

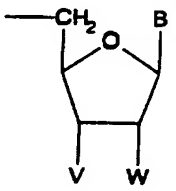
R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

m is 1 to 3;

n is 0 to 2; and

Z is a moiety of the Formula V,



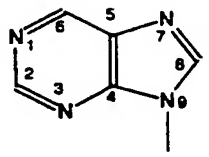
(V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

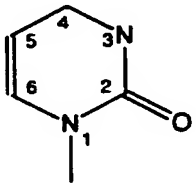
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with =O -OH, -SH, $-NH_2$, or halogen, at position 4 with NH_2 or =O, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII

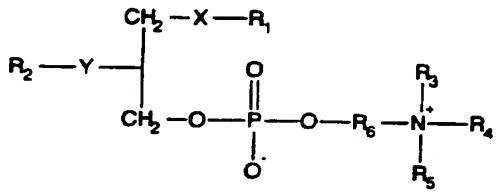


(VII)

substitued at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.

102. A compound according to Claim 101, in combination with a pharmaceutical carrier.

103. A method of combating tumors in a subject in need of such treatment comprising administering to said subject an effective amount of a compound of Formula I



(I)

wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

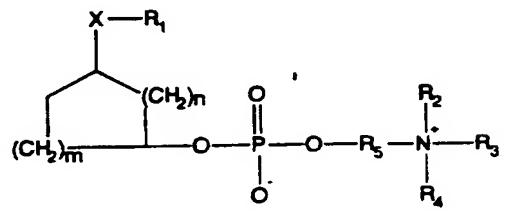
Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_6 is a branched or unbranched C_2 to C_6 alkyl group; and

R_3, R_4, and R_5 are independently methyl or ethyl, or R_3 and R_4 together form an aliphatic or heterocyclic ring having five or six members and R_5 is methyl or ethyl;

or a pharmaceutical salt thereof.

104. A method of combating tumors in a subject in need of such treatment comprising administering to said subject an effective amount of a compound of Formula II:



(II)

wherein: the ring structure of Formula II is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl;

R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group;

R_2, R_3, and R_4 are independently methyl or ethyl, or wherein R_2 and R_3 together form an aliphatic or heterocyclic ring having five or six members and R_4 is methyl or ethyl;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

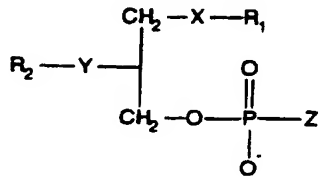
R_5 is a branched or unbranched C_2 to C_6 alkyl group;

m is 1 to 3; and

n is 0 to 2;

or a pharmaceutical salt thereof.

105. A method of combating tumors in a subject in need of such treatment comprising administering to said subject an effective amount of a compound of Formula III



(III)

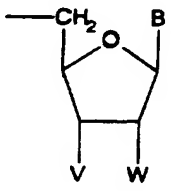
wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; and

Z is a moiety of the Formula V,



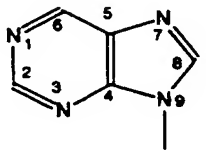
(V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

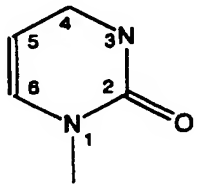
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with =O -OH, -SH, $-NH_2$, or halogen, at position 4 with NH_2 or =O, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII

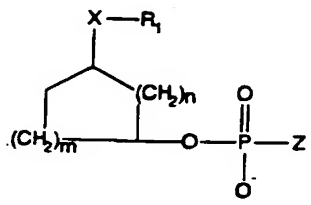


(VII)

substitued at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen;

or a pharmaceutical salt thereof.

106. A method of combating tumors in a subject in need of such treatment comprising administering to said subject an effective amount of a compound of Formula IV:



(IV)

wherein: the ring structure of Formula IV is optionally substituted from 1 to 3 times with C_1 to C_3 alkyl;

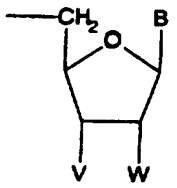
R_1 is an unbranched or branched, saturated or unsaturated C_6 to C_{20} alkyl group;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

m is 1 to 3;

n is 0 to 2; and

Z is a moiety of the Formula V,



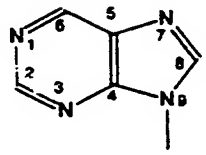
(V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

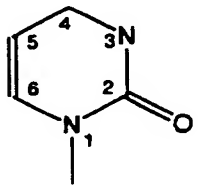
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with =O -OH, -SH, $-NH_2$, or halogen, at position 4 with NH_2 or =O, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII



(VII)

substitued at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.

or a pharmaceutical salt thereof.

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A3

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08/314,901	29 September 1994 (29.09.94)	US

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(74) Agent: WOESSNER, Warren, D.; Schwegman, Lundberg & Woessner, P.O. Box 2938, Minneapolis, MN 55402 (US).

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Published

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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 13 June 1996 (13.06.96)

(54) Title: LIPID ANALOGS FOR TREATING VIRAL INFECTIONS

(57) Abstract

A method of treating viral infections, and in particular HIV-1, hepatitis B virus, and herpesviruses, is disclosed. The method comprising administering to a subject in need of such treatment an infection-combating amount of a phospholipid or phospholipid derivative.

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INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/US 95/10111

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/685 A61K31/675 C07F9/10 C07H19/10 C07H19/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07F C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	DE,A,39 34 820 (BOEHRINGER MANNHEIM) 25 April 1991 see page 2, line 50 - page 3, line 5 see page 5, last paragraph ---	1-52, 85-91, 103
Y	J.MED.CHEM., vol.34, no.4, 19 October 0 pages 1377 - 83 'In vitro evaluation of phosphocholine and quaternary ammonium containing lipids as novel anti-HIV agents' see page 1377, left column, line 26 - line 38 --- -/--	103

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

3

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 1996	29.04.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	GERLI, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	AIDS RES. HUM. RETROVIRUSES, vol.11, no.6, 5 pages 705 - 712 'Membrane interactive phospholipids inhibit HIV type 1-induced cell fusion and surface gp160/gp 120 binding to monoclonal antibody' see page 705 ---	1-52
Y	DE,A,40 10 228 (MÜLLER) 2 October 1991 see claim 1 ---	1-20, 35-40, 85-91
A	WO,A,91 09602 (BOEHRINGER MANNHEIM) 11 July 1991 see the whole document -----	1-20, 35-40, 45-72, 85-91, 103

INTERNATIONAL SEARCH REPORT

Ir. ational application No.
PCT/US95/10111

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see remark on the enclosed sheets!

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. claims 1-20,35-40-,47-52,85-91,103
2. claims 21-34,41-46,53-58,92-98,104
3. claims 59-84,99-102,105,106

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1. claims 1-20,35-40,47-52,85-91,103

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

REASONED STATEMENT

Compounds of four different structural formulas I to IV and their different medical uses are claimed.
The ISA has checked whether there is a priori a technical relationship among the four formulas in the form of a single characteristic subunit appearing in all formulas I to IV.
The only common subunit is the substituted phosphoric group.
The common inventive concept underlying claims 1-106 is therefore the provision of new antiviral compounds characterised by a substituted phosphoric group.

This concept is not novel in view of all documents cited in the partial search report. All these documents disclose compounds having a substituted phosphoric group, their pharmacological activities, and their use in medicine, in particular in the treatment of viral diseases and cancer (cf. passages cited in the search report). These documents not only anticipate the subunit common to all formulas I to IV, but also the substructure of phosphatidylcholine, common to formulas I and II.

In this situation the structures (I), (II), and (III + IV) are regarded, a posteriori, as belonging to three different inventive concepts.

In absence of an alternative technical feature common to all claims 1-106 in the sense of Rule 30 EPC, i.e. having the meaning of a common special technical feature defining a contribution over the prior art, the compounds of the different structural formulas (I), (II), and (III + IV) (together with their relevant medical uses) represent three different inventions, as listed in the communication pursuant to Article 17(3)a PCT.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The present search has been limited to the first listed invention. Covering all the other subjects in a single search would have caused major additional searching efforts.

Should a search fee be paid for the third invention, it cannot be ruled out that, in presence of prior art anticipating a characteristic substructure common to the two formulas III and IV, a further unity objection will be raised, dividing the claimed subject matter relating to formula III from that relating to formula IV.

- -

YES : claims 1-20, 35-40, 47-52, 85-91, 103

Compounds of formula I per se; their use in the manufacture of medicaments for combating viral infection, for inhibiting the production of hepatitis B virus antigen, for inhibiting the incorporation of HIV-1 major glycoprotein gp120 into a cell membrane of a subject infected with HIV-1, and for combating tumors.

NO : claims 21-34, 41-46, 53-58, 92-98, 104

Compounds of formula II per se; their use in the manufacture of medicaments for combating viral infection, for inhibiting the production of hepatitis B virus antigen, for inhibiting the incorporation of HIV-1 major glycoprotein gp120 into a cell membrane of a subject infected with HIV-1, and for combating tumors.

NO : claims 59-84, 99-102, 105, 106

Compounds of formulas III and IV per se; their use in the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

manufacture of medicaments for combating viral infections and for combating tumours.

Remark:
Although claims 1-84, 103-106 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried on and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Interna... l Application No
PCT/US 95/10111

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-3934820	25-04-91	AU-B- 6529190	16-05-91
		WO-A- 9105558	02-05-91
DE-A-4010228	02-10-91	NONE	
WO-A-9109602	11-07-91	DE-A- 3942933	27-06-91
		AU-B- 8004291	24-07-91
		DE-D- 59005139	28-04-94
		EP-A- 0506704	07-10-92

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